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Physiological Responses of Heart Failure Patients to Exercise: Focus on Blood Lactate

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Review Paper

Physiological Responses of Heart Failure Patients to Exercise:

Focus on Blood Lactate

Abstract

This review paper looks at blood lactate responses of heart failure (HF) patients during exercise, in comparison to healthy individuals and following exercise training. HF patients exhibit significantly higher lactate levels compared to healthy controls during sub-maximal exercise at the same workloads. Exercise training can significantly reduce these lactate levels at matched sub-maximal workloads in HF patients. Resting lactate levels in HF patients are generally no different to healthy individuals, but patients with lower functional capacity due to more advanced HF may exhibit higher levels. There is no evidence of resting lactate levels being reduced following exercise training. Lactate levels at peak exercise capacity are significantly lower in HF patients compared to healthy individuals. No significant differences in peak lactate levels have been noted following endurance exercise training, although significant increases in peak lactate have been seen following a combined endurance/resistance exercise programme. Although there is lots of published data on blood lactate levels during laboratory-based exercising testing in this patient group, to date there appears to be no published data of blood lactate levels in HF patients in an applied setting, i.e. during cardiac rehabilitation exercise sessions.

Introduction

Heart failure (HF), sometimes referred to as chronic heart failure or congestive heart failure, can be described as a reduction in cardiac output, such that the demands of the vital organs and physiological systems of the body are often unable to be met (American Association of Cardiovascular and Pulmonary Rehabilitation, 2004).

The condition is complex and multisystem in nature, with compensatory mechanisms involving the whole body being brought into play to counteract the reduction in cardiac function. Although initially helpful, over the long-term these compensatory mechanisms cause damage to the vital organs and lead to patients exhibiting the most common symptoms of muscular fatigue and dyspnoea (Piepoli et al, 2010), resulting in exercise intolerance and consequent reduction in quality of life (Chung & Schulze, 2011). Exercise intolerance is often one of the first symptoms that HF patients exhibit and is therefore inextricably linked to its diagnosis (Piña et al, 2003), as well as classification of severity (Table 1. McMurray et al, 2012).

Table 1. New York Heart Association (NYHA) functional classification

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in undue breathlessness, fatigue or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Piepoli (2013) states that there is compelling evidence that skeletal muscle dysfunction plays an important role in exercise intolerance in HF, with Middlekauf (2010) going further by making the case for it being the *major* limitation. Reduced

capillary and mitochondrial density, reduced oxidative enzymes and conversion of type I (oxidative, fatigue-resistant) muscle fibres to type IIb (glycolytic, fatigue-prone) all contribute to the early onset of anaerobic metabolism and the consequent accumulation of blood lactate during exercise (Piepoli, 2013). Blood lactate can therefore be argued to be an important metabolic marker of exercise intolerance in HF patients. This review will summarise the research findings to date relating to blood lactate responses in this patient group, while briefly discussing other physiological responses relevant to these findings.

Haemodynamics and blood lactate response in HF

Wilson, Martin, Schwartz & Ferraro (1984) claim to have provided the first direct evidence that maximal exercise capacity in HF patients is limited by inadequate nutritive flow to the skeletal muscles. In three groups of patients, with normal, moderately reduced and markedly reduced maximal oxygen uptake (VO_{2max}), a number of haemodynamic and metabolic measurements were made during a maximal cycling exercise test. The investigators noted that with decreasing VO_{2max} , the groups' also exhibited decreased cardiac output, decreasing leg blood flow and decreasing maximal leg VO_2 at maximal exercise capacity. However, leg oxygen (O_2) extraction and venous (femoral) lactate concentrations were seen to increase in patients with diminished exercise capacities. Patients who terminated exercise due to fatigue had higher levels of venous lactate concentrations and O_2 extraction compared to other patients at the same workload who were not fatigued. Interestingly, all three groups had similarly elevated femoral-arterial lactate gradients and leg O_2 extraction at exercise

termination, which, the investigators suggest, might mean that a critical level of muscle under-perfusion was reached.

Although the main focus of Sullivan, Higginbotham and Cobb's (1988) study was investigating haemodynamics, the authors claim to have been one of the first studies to demonstrate reduced blood lactate concentrations in HF patients following a 4-6 month period of cardiovascular training. Although they found no change in arterial and venous (femoral) blood lactate at rest and peak exercise following the exercise programme, the authors reported a marked decrease in blood lactate at sub-maximal exercise intensities in both arterial and venous samples. As cardiac output was unchanged following exercise training the investigators postulated that peripheral metabolic or vascular factors were more important than central haemodynamics in determining the onset of lactic acid production. However, it is worth noting that leg blood flow was unchanged at sub-maximal workloads following exercise training.

A further study by Sullivan and colleagues (Sullivan, Knight, Higginbotham and Cobb, 1989) looked at the differences in central and peripheral blood flow between HF patients and healthy controls at rest and during a symptom-limited exercise test using cycling ergometry. No significant difference was seen between the two groups in arterial and venous (femoral) lactate at rest (both $\sim 1.0 \text{ mmol}\cdot\text{l}^{-1}$). However, as in their previous study, lactate increased at an accelerated rate in HF patients during the exercise test. At peak exercise, venous lactate was significantly lower in HF patients ($\sim 8.4 \text{ mmol}\cdot\text{l}^{-1}$) compared to healthy participants ($\sim 11.5 \text{ mmol}\cdot\text{l}^{-1}$), due to the attainment of much lower work rates. Peak oxygen consumption ($\text{VO}_{2 \text{ peak}}$) was also significantly lower ($p < 0.001$) in the HF group ($15.1 \pm 4.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) compared to the healthy participants ($32.1 \pm 9.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Leg blood flow was less in HF patients than

controls at rest, sub-maximal and maximal intensities. Local vascular resistance in the exercising limbs of HF patients was greater than healthy participants at rest and during sub-maximal and peak exercise, with non-leg blood flow being preferentially maintained. This finding, along with a decreased level of oxygen consumption in the legs of HF patients, was suggested to be evidence for reduced muscle perfusion being an important factor in the early onset of anaerobic metabolism in HF patients during exercise.

A further study by Sullivan and Cobb (1990) investigated changes in blood lactate levels in HF patients following a 4-6 month period of cardiovascular exercise training (at 75% $\text{VO}_2 \text{ max}$). Both arterial and venous (femoral) lactate levels were significantly lower during sub-maximal exercise following the training period, despite no improvements being seen in leg blood flow, O_2 delivery or leg VO_2 at sub-maximal exercise. The investigators suggested that skeletal muscle adaptations may be responsible for the delayed rise in lactate demonstrated in this study. Sullivan and Cobb also reported no differences in resting and peak lactate levels following the exercise training (values not reported). Findings from this paper will be discussed further during the 'anaerobic threshold and lactate responses' section.

Sullivan, Green & Cobb (1991) confirmed their earlier findings (Sullivan et al, 1989) of lower leg blood flows and accelerated rates of blood lactate accumulation in HF patients compared to controls. The main focus of this study was skeletal muscle metabolism, and as such it will be reviewed in more detail in the next section.

Lactate threshold in relation to haemodynamics was the focus of a study by Yamabe, Itoh, Yasaka, Takata and Yokoyama (1994). These investigators looked at the rate of O_2 delivery compared to O_2 consumption, both centrally and in the exercising

legs (during supine cycling), above and below the anaerobic threshold using arterial lactate sampling. Yamabe et al report that centrally the rate of increase in O_2 delivery versus the increase in VO_2 was reduced above the anaerobic threshold due to a reduced stroke volume. However, measurements in the legs did not differ above or below anaerobic threshold. Yamabe et al believe their findings demonstrate that leg blood flow is maintained at the expense of non-leg blood flow in HF patients with reduced cardiac output, thus contradicting the concept that lactate threshold occurred at the onset of insufficient O_2 supply. They suggest that decreased hepatic blood flow may be one mechanism for decreased lactate clearance and consequently a lowered lactate threshold in HF patients. The investigators also reported arterial lactate levels during the exercise test for NYHA classes I, II and III, with no significant differences between classes noted at rest (range $0.8 - 0.96 \text{ mmol l}^{-1}$) or lactate threshold (range $1.49 - 1.88 \text{ mmol l}^{-1}$). However peak arterial lactate values were significantly different ($p < 0.001$) between NYHA classes, with values reducing with decreased functional capacity classification (NYHA I $6.3 \pm 2.14 \text{ mmol l}^{-1}$, NYHA II $4.47 \pm 1.59 \text{ mmol l}^{-1}$, NYHA III $3.58 \pm 0.92 \text{ mmol l}^{-1}$).

A much later study by Hambrecht et al (1997), although focussing primarily on structural changes in skeletal muscle following exercise training, also measured changes in leg blood flow and venous (femoral) lactate levels following a comprehensive and committing six month programme. Hambrecht reported no relationship between leg blood flow and venous lactate both before and after the exercise training programme, in accordance with the Sullivan et al (1988) findings. These findings seem at odds with Sullivan et al (1989) findings regarding the importance of reduced perfusion in the early onset of anaerobic metabolism, but

Hambrecht suggested that their findings did not rule out the importance of reduced leg blood flow, but did suggest that other mechanisms were involved.

Skeletal muscle metabolism and blood lactate response in HF

Unsurprisingly, the largest area of research concerning blood lactate responses in HF is that of skeletal muscle metabolism. Sullivan et al (1991) compared skeletal muscle metabolism, using muscle biopsies of the vastus lateralis, and blood lactate responses (arterial and venous) of HF patients with healthy controls during maximal cycling exercise. Once again, no difference was noted in resting lactate levels between the groups, but HF patients exhibited higher levels at sub-maximal intensities. See Table 2.

Table 2. Venous (femoral) lactate levels (mmol l^{-1}) in HF patients and controls during rest and cycling exercise.

	Patients	Controls	Significance
Rest	1.1 ± 0.7	0.9 ± 0.5	NS
50W	4.2 ± 1.5	1.7 ± 0.7	$p < 0.001$
Peak	7.6 ± 3.2	12.3 ± 3.1	$p < 0.01$

NS = not significant

At peak exercise, lower lactate levels and higher phosphocreatine (PCr) levels were seen in HF patients, suggesting that lactate accumulation and PCr depletion were not limiting factors to exercise. Instead the investigators reported an inverse relationship between resting citrate synthetase activity and submaximal lactate levels ($r=0.74$, $p<0.05$), suggesting that reduced aerobic enzyme activity is at least partly responsible for lowered exercise tolerance. It was also noted that the skeletal muscle to arterial blood gradient was not altered in the HF patients compared to healthy subjects,

suggesting that the mechanisms that mediate removal of the lactate from the muscle to arterial blood are not over-whelmed in this patient group.

Hambrecht et al (1995) reported that venous (femoral) lactate levels were significantly reduced during sub-maximal exercise in HF patients compared to controls ($p < 0.05$), following six months of cardiovascular exercise training. However no change was seen in resting and peak exercise values (see Table 3 for HF group lactate levels). The change in sub-maximal levels was thought to be due to the 33% increase in aerobic capacity observed following the training period, which was closely linked to changes in the oxidative capacity of the working skeletal muscles. High correlations were reported between increased VO_2 at peak exercise ($r = 0.87$) and ventilatory threshold ($r = 0.82$) with increases in skeletal muscle mitochondria.

Table 3. Lactate levels for HF patients during a symptom-limited cycle exercise test, pre- and post-training.

	Rest	50W	75W	100W	Peak
Pre-training lactate ($\text{mmol}\cdot\text{l}^{-1}$)	~1.0	~1.8	~2.9	~4.2	~7.2
Post-training	~0.8	~1.2	~1.6	~3.5	~7.0

Data extrapolated from published graphs.

High correlations were also reported by Belardinelli, Georgiou, Scooco, Barstow and Purcaro (1995) between mitochondrial density and changes in peak VO_2 ($r = 0.77$), and between mitochondrial density and increases in lactate threshold ($r = 0.81$), following low intensity exercise training. This study is discussed in more detail later in this review.

In a later study, Hambrecht et al (1997) observed that following exercise training venous (femoral) lactate levels during submaximal exercise were shown to be inversely correlated with the volume density of mitochondria ($r = -0.58$) and the

surface density of mitochondrial cristae ($r=-0.48$). An increase in oxidative enzyme activity and a 'reshift' from type II to type I fibres was also observed. These changes were thought to be unrelated to changes in peripheral perfusion.

A study by Schaufelberger, Eriksson and Swedberg (1996) focussed on the availability of energetic substrates and oxidative enzyme availability in the skeletal muscle of HF patients. In this study the decreased activity of oxidative enzymes were thought to contribute to the early onset of anaerobic metabolism. Both citrate synthase and 3-Hydroxyacyl-CoA were significantly lower in patients than controls and citrate synthase was inversely correlated ($r=-0.90$) with skeletal muscle lactate at anaerobic threshold. The investigators also reported that energetic compounds were unlikely to be a limiting factor in exercise capacity in HF; adenosine triphosphate, creatine phosphate and glycogen levels were all higher in patients at maximal exercise capacity. In contrast with earlier studies, peak venous lactate levels were not significantly lower in patients than controls (patients $7.9 \pm 3.3 \text{ mmol l}^{-1}$, controls $8.4 \pm 2.4 \text{ mmol l}^{-1}$), but capillary lactate samples were lower in patients than controls (patients $4.7 \pm 1.3 \text{ mmol l}^{-1}$, controls $6.2 \pm 1.5 \text{ mmol l}^{-1}$). In this study resting lactate levels were reported to be higher in patients than controls, which was in contrast to earlier studies by Sullivan and colleagues (Sullivan et al, 1989; Sullivan et al, 1991). However, on closer examination, the reported data appears contradictory. It appears that only the fingertip capillary lactate levels were higher in patients at rest (patients $2.2 \pm 0.9 \text{ mmol l}^{-1}$, controls $1.7 \pm 0.4 \text{ mmol l}^{-1}$) as femoral vein levels did not differ between the groups (both 1.6 mmol l^{-1}).

Andrews, Walsh, Evans and Cowley (1997) looked at the blood lactate responses of HF patients compared to healthy controls during forearm exercise of

differing intensities, by sampling venous blood that directly drained the working muscle. Andrews et al reported significantly higher ($p = 0.002$) lactate levels at rest in the NYHA III group ($1.18 \text{ mmol}\cdot\text{l}^{-1}$) than controls ($0.65 \text{ mmol}\cdot\text{l}^{-1}$). The NYHA II group resting levels ($0.84 \text{ mmol}\cdot\text{l}^{-1}$) were not significantly different to controls, but were significantly different ($p = 0.01$) to the NYHA III group. In contrast to other studies, the HF patients in the NYHA III group exhibited higher lactate levels at volitional exhaustion ($3.31 \pm 0.26 \text{ mmol}\cdot\text{l}^{-1}$) group compared to controls ($2.56 \pm 0.16 \text{ mmol}\cdot\text{l}^{-1}$). The authors suggested that their resting lactate results show that skeletal muscle is already stressed when in a resting state, something which they hadn't been expecting and had not previously been reported. Andrews et al do not comment directly on the difference in peak lactate values in their study compared to those previously reported, but do allude to their unique sampling method giving different results to others, due to a lack of dilution from non-skeletal muscle tissues. Perhaps their differing results may also be due to the use of smaller muscle groups.

Näveri , Leinonen, Kiilavuori and Härkönen (1997) looked at lactate levels in venous (forearm) blood and skeletal muscle (quadriceps femoris) in their muscle biopsy study. Although no data were reported on resting venous blood lactate levels, the authors did find that skeletal muscle lactate tended to be higher in HF patients, although the difference wasn't reported as significant. As in previous studies, peak blood lactate levels were significantly higher ($p < 0.001$) in the control group ($5.2 \pm 0.6 \text{ mmol}\cdot\text{l}^{-1}$) compared to HF patients ($2.2 \pm 0.3 \text{ mmol}\cdot\text{l}^{-1}$) following maximal cycling exercise, with the difference remaining similar 10 minutes (mins) after exercise. However, an interesting finding was that *skeletal* muscle lactate levels at peak capacity were similar in both groups. The authors point out that blood lactate differences are

most likely due to the lesser amount of work performed by the HF group and the reduced skeletal muscle perfusion impairing the rate of diffusion from the muscle to the bloodstream. Lower levels of the skeletal muscle enzyme alpha-ketoglutarate dehydrogenase in HF patients compared to controls (48% less), led the investigators to conclude that aerobic energy production is impaired due to a lack of aerobic enzymes, leading to the early lactate acidosis seen in HF patients.

Anaerobic threshold and blood lactate response in HF

The reproducibility of anaerobic threshold measurements in HF patients was investigated by Weber and Janicki (1985), using breath-by-breath gas analysis and mixed venous lactate samples (from the pulmonary artery) during incremental treadmill exercise to exhaustion. Anaerobic threshold was considered to be the VO_2 corresponding to a fixed lactate value of 12mg/100ml ($1.34 \text{ mmol}\cdot\text{l}^{-1}$) and was reported to be reproducible, in the small number of patients ($n=8$) who were tested twice in the same day ($r=0.92$). The investigators also report that anaerobic threshold was reproducible the following day in a small sub-group of patients ($n=8$), who had received amrinone therapy, but whose cardiac output response to exercise had been unchanged after receiving the drug. A number of patients ($n=12$) whose cardiac output response to exercise *had* been improved after receiving amrinine therapy, were seen to have a retarded rate of lactate increase, with anaerobic threshold being delayed by at least one exercise stage. Weber and Janicki also report that the anaerobic threshold at the fixed lactate value was exceeded at lower absolute VO_2 levels with increasing HF severity (categorised by the investigators as class A [mild, $\text{VO}_2 \text{ max} > 20 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to

D [severe, $< 10 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$]), but in all categories the anaerobic threshold occurred at 60-70% of individual $\text{VO}_{2 \text{ max}}$.

Weber and Janicki also investigated the response of HF patients to sub-maximal endurance exercise at intensities that were described as 'aerobic' and 'anaerobic'. A very small sample ($n=5$) of patients exercised 'aerobically' at 60% of $\text{VO}_{2 \text{ max}}$ and were able to complete the 20 minutes of exercise without undue fatigue, breathlessness or a significant change in blood lactate from resting values ($0.72 \text{ mmol}\cdot\text{l}^{-1}$). Whereas the patients ($n=4$) exercising 'anaerobically' at around 92% $\text{VO}_{2 \text{ max}}$ completed only 10.6 minutes due to dyspnea and fatigue, with lactate levels steadily increasing to $2.93 \text{ mmol}\cdot\text{l}^{-1}$.

Itoh, Koike, Taniguchi and Marumo (1989) built on the findings of Weber and Janicki when they investigated the use of anaerobic threshold measurements in HF patients as an objective means of evaluating the severity of the disease. The authors used a 'rapidly responding gas analysis system', a relatively new technology at the time, to measure ventilatory anaerobic threshold. These measurements were compared to anaerobic threshold measurements obtained using the invasive method of arterial (brachial) lactate sampling. There was no significant difference in VO_2 values at anaerobic threshold between the two methods (ventilatory threshold $13.4 \pm 2.7 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$, lactate threshold $13.3 \pm 2.7 \text{ mmol}\cdot\text{l}^{-1}\text{ml}\cdot\text{kg}\cdot\text{min}^{-1}$) and a very high correlation ($r=0.93$) between the two. Itoh et al report that both anaerobic threshold and $\text{VO}_{2 \text{ peak}}$ decrease with increasing HF severity, when expressed as a percentage of age and sex predicted values. The authors suggest that anaerobic threshold may be a better means of evaluating exercise intolerance than $\text{VO}_{2 \text{ peak}}$ measurement as it is unaffected

by patient motivation or the philosophy of personnel supervising an exercise test as to when to terminate the test.

Another study looking to validate the use of anaerobic threshold measurements by gas exchange in HF patients was that of Sullivan and Cobb (1990), from which some of the lactate data has been discussed earlier in this review. The investigators reported that anaerobic threshold as measured by gas exchange, determined by the ventilatory equivalents method, occurred after relatively small rises in arterial lactate (patients $0.9 \pm 0.4 \text{ mol l}^{-1}$, controls $0.8 \pm 0.5 \text{ mol l}^{-1}$) above resting values (not reported), in both HF patients and controls.

A much more recent paper by Beckers et al (2012) demonstrates the changes in understanding with regards to anaerobic threshold measurement since the aforementioned studies were conducted. The reader is referred to Binder et al (2008) for a thorough review of this area. Beckers and colleagues compared three different methods of identifying anaerobic threshold for the purpose of safely prescribing higher exercise intensities (90-100% anaerobic threshold) to HF patients. The methods compared were: respiratory compensation point (RCP), which was defined as the inflection in the minute ventilation/expired carbon dioxide (VE/VCO_2) relationship and considered by the investigators to be the gold standard method; heart rate turn point (H RTP), defined as the heart rate (HR) at the transition from the linear HR-workload relationship to the curvilinear; and lactate turn point two (LTP2), defined as the second lactate threshold at a specific inclination of the lactate curve. Unlike older studies reported here, lactate sampling was carried out using capillary blood collected from the earlobe. Following a symptom-limited cycling exercise test using a ramp protocol, the HR, workload and VO_2 were compared at RCP (the gold standard method), with

H RTP and LTP2. The investigators report that no differences were seen in the aforementioned parameters at RCP and H RTP. However, VO_2 , HR and workload were all significantly higher ($p < 0.0001$) when measured at LTP2 than RCP (9%, 5% and 12% respectively). Beckers et al conclude that training at exercise intensities equivalent to LTP2 may overload the patient due to the reduction in left ventricular ejection fraction previously shown in patients exercising above the LTP2.

The effects of training on blood lactate response in HF

The findings of a number of studies (Sullivan, Higginbotham and Cobb (1988); Sullivan and Cobb (1990); Hambrecht et al (1995); Hambrecht et al (1997)) concerning the lactate responses of HF patients following exercise training have already been presented earlier in this review and their findings will not be duplicated here. The remaining studies will now be summarised.

Belardinelli et al (1995) evaluated the effects of lower intensity exercise training on HF patients. Lactate threshold was determined by ventilatory threshold and lactate inflection point before and after an eight week training period, at an intensity of $\sim 40\% \text{VO}_2 \text{ max}$. No significant differences in resting or peak plasma lactate (from antecubital vein) were seen following the training period. However there was a marked and significant decrease in plasma lactate at submaximal intensities, with lactate threshold being delayed from 560 ± 85 to $720 \pm 102 \text{ ml} \cdot \text{min}^{-1}$ of VO_2 , amounting to a 20% increase in lactate threshold. The investigators also reported high correlations between ventilatory and lactate thresholds both before ($r=0.94$, $p < 0.0001$) and after ($r=0.95$, $p < 0.0001$) the exercise training. The investigators concluded that significant improvements in functional capacity can be achieved by training at this lower exercise

intensity, rather than the higher intensities (70-80% VO_2 max) used in some previous studies.

A couple of studies by Tyni-Lenné and colleagues evaluated the effects of training using a smaller muscle mass. Tyni-Lenné, Gordon, Jansson, Bermann, and Sylven (1997) investigated the effects of eight weeks of intensive knee extensor training on women with HF during a randomised crossover study. A symptom-limited incremental test of bilateral knee extensor exercise revealed increases in peak work rate (43% $p < 0.0001$) and VO_2 peak (14% $p < 0.0005$) following the exercise training. The investigators also reported a 17% reduction in blood lactate (from antecubital vein) during a 15 min. submaximal (65% VO_2 peak) exercise test and recovery.

Tyni-Lenné, Gordon, Jensen-Urstad, Dencker, Jansson, and Sylven (1999) went on to compare exercise training involving minor and major muscle mass in HF patients who had previously participated in exercise training. Exercising patients were randomly allocated to knee extensor training or cycling exercise groups and trained for eight weeks at the same exercise intensities for both groups (50% peak work rate, increasing to 60-70% from week 5). In both exercising groups, lactate levels (from antecubital vein) decreased during submaximal exercise (cycle training $p < 0.4$, knee extensor training $p < 0.009$), but no significant difference was reported in peak lactate levels (see Table 4). However, peak lactate data from the graphs published in this paper seem to differ from those shown in table form, so there is some doubt about the actual levels.

Table 4. Peak blood lactate concentrations before and after exercise training.

	Cycle training group		Knee extensor group	
	Before	After	Before	After
Lactate (mmol·L ⁻¹)	2.63 ± 0.77	2.38 ± 0.87	3.74 ± 2.4	3.39 ± 1.5

Differences before and after training were non-significant in both groups.

Although peak work rate increased in both groups following training, only in the knee extensor training group did VO₂ peak increase significantly (19% $p < 0.1$). Significant increases in the oxidative enzyme citrate synthase following training were also reported in both groups (cycling 23% $p < 0.2$, knee extensor training 45% $p < 0.008$). It appears that the level of significance used in this study must differ from the more usual ($p \leq 0.05$).

The study by Larsen, Aarsland, Kristiansen, Haugland and Dickstein (2001) investigated the use of differing exercise protocols in order to assess the efficacy of an exercise training programme in HF patients. Lactate sampling was used in two of the three exercise protocols examined, which were: 1) a maximal cycling test using a ramp protocol, with gas exchange measurements and arterial lactate sampling; 2) a 30 min. treadmill endurance test at 85% of HR peak, with capillary blood lactate sampling (collection site not specified); 3) a 6 minute walk test. All participants completed the three exercise protocols before and after a 12 week training period of cardiovascular exercise at 80% HR_{peak}. Following the training period significant improvements were seen in 6 minute walk distance (+8.1%, $p < 0.001$) and peak work rate during maximal cycling (+ 44.6%, $p < 0.001$), but no significant differences were seen in VO_{2 peak} or peak arterial lactate during the maximal cycling test. Employing the 30 min. treadmill endurance protocol, significant improvements were seen in treadmill distance (+ 6.8%, $p < 0.05$) and capillary lactate, measured as area under the curve (-19.0%, $p < 0.005$).

Maximal, peak (end of test) and recovery capillary lactate levels all showed non-significant reductions (see Table 5).

Table 5. Blood lactate concentrations during and after a 30 min. treadmill endurance protocol, before and after cardiovascular exercise training.

	Pre-training	Post-training	% Difference	<i>P</i>
Lactate area under the curve (mmol·l ⁻¹)	45.19 ± 14.46	36.45 ± 14.27	-19.5	<i>p</i> < 0.005
Maximal lactate (mmol·l ⁻¹)	2.25 ± 0.59	1.95 ± 0.96	- 13.0	NS
Peak (end of test) lactate (mmol·l ⁻¹)	1.98 ± 0.58	1.70 ± 0.75	- 14.6	NS
Recovery (5 mins post) lactate (mmol·l ⁻¹)	1.71 ± 0.75	1.59 ± 0.92	- 6.7	NS

NS = non-significant difference.

The investigators suggest that endurance testing involving lactate sampling may be the more sensitive and appropriate protocol for demonstrating the efficacy of exercise training programmes in HF patients, particularly in relation to reduced lactate production at matched work intensities, which demonstrates a reduced reliance on anaerobic metabolism.

Delagardelle, Feiereisen, Autier, Shita, Krecke and Beissel (2002) investigated the efficacy of endurance training compared to combined strength/endurance training in HF patients following a 40 session training period. Endurance training consisted of alternating 2 mins. intervals of cycling exercise at 50% VO₂ peak and 75% VO₂ peak for 40 mins. While the combined training consisted of 20 mins. of the endurance training intervals, with 20 mins of strength training (3 sets of 6 large muscle group exercises at 60% of one-repetition maximum). A symptom-limited cardiopulmonary cycling exercise test with capillary (earlobe) lactate sampling before and after the training

period revealed significant increases in peak lactate for the combined training group (+25%), with a small but non-significant decrease (-4.8%) in the endurance training group (see Table 6). Working capacity was increased in both groups (endurance training +10.4%, combined training + 15.6%), while VO_2 peak only increased the combined group (+7.8%, not significant). Strength and left ventricular function parameters also showed improvements in the combined training group only, leading the authors to recommend combined strength/endurance training as the preferred modality for HF patients.

Table 6. Blood lactate concentrations before and after 40 sessions of endurance training or combined strength/endurance training.

	Baseline	Following training	Difference
Lactate - endurance training group ($\text{mmol}\cdot\text{L}^{-1}$)	4.90	4.57	- 4.8% (NS)
Lactate - combined training group ($\text{mmol}\cdot\text{L}^{-1}$)	3.87	4.74	+ 25% *

NS = non-significant difference. * $p < 0.05$

Other studies relating to blood lactate response in HF

A couple of studies do not fit neatly into any of the aforementioned categories and so are presented separately here.

Wensel et al (2005) investigated the causes of hyperventilation, which is characteristic of HF patients and had previously been thought to be due to the early development of systemic lactic acidosis during exercise. This hyperventilation causes a fall in the partial pressure of arterial CO_2 (pCO_2) to below the levels seen in normals. The relationship between minute ventilation and amount of CO_2 expired during exercise (VE/VCO_2 slope) is a marker of excess ventilation and a high VE/VCO_2 slope

has also recently been shown to be a significant prognostic indicator in HF patients (Sarullo et al, 2010). Wensel and colleagues found that both $p\text{CO}_2$ and VE/VCO_2 slope were not related to arterial lactate at peak exercise in HF patients. Furthermore, during early recovery from exercise a decline in hyperventilation was seen, despite a rise in systemic acidosis. Patients with greater hyperventilation and higher VE/VCO_2 slope values had greater increases in systemic lactate during early recovery and this was thought to be indicative of greater quantities of lactate being 'trapped' within the muscles during exercise. The investigators believe their findings present a strong case for systemic lactic acidosis *not* being the cause of hyperventilation in HF patients. Instead they make the case for *skeletal muscle* acidosis being a potent stimulus for hyperventilation, possibly due to skeletal muscle ergoreflex activation.

And finally, a recent paper by Melenovsky et al (2012) looked at the subject of energetic substrate availability in HF patients with and without type 2 diabetes, alongside healthy controls. Baseline venous (forearm) blood lactate was reported to be similar in all groups ($1.27 - 1.30 \text{ mmol}\cdot\text{l}^{-1}$). However, in contrast to previous studies, following a maximal cycling exercise test peak lactate levels were reported to rise similarly (9-14%) in all groups ($1.40 \text{ mmol}\cdot\text{l}^{-1}$ for controls, $1.44 \text{ mmol}\cdot\text{l}^{-1}$ for both HF groups). These peak lactate values seem unusually low compared to other studies. This may be due to the time taken to obtain the samples following the exercise test (1-3 mins). Or perhaps the low levels were due to the type of analysis; serum samples were frozen until analysis by colorimetric assay. The investigators do not comment on the low lactate levels reported, however it could perhaps be related to levels of circulating catecholamines, which were not different in HF patients compared to controls. The investigators believe the catecholamine findings may reflect the more intensive

pharmacological therapy (beta-blockers and angiotensin-converting enzyme inhibitors) being prescribed to these patients than in studies from the pre-beta-blocker era. Given that strong positive relationships between lactate and the catecholamines epinephrine/norepinephrine during exercise has been reported by Belardinelli et al (1995) and Tyni-Lenné et al (1999), perhaps this may be at least a partial explanation as to why no differences were seen in lactate levels between HF patients and healthy controls in this study.

Conclusion

It is clear from the research findings reviewed that HF patients accumulate blood lactate at lower absolute workloads compared to healthy individuals and there is some evidence that this reliance on anaerobic metabolism at low workloads does seem to be exaggerated with increasing disease severity (Weber & Janicki, 1985). However, a closer look at the data reveals that the anaerobic threshold (AT) of HF patients occur at relatively *high* percentages of overall working capacity or $VO_{2\text{ max}}$. Weber and Janicki report AT occurring at around 60-70% $VO_{2\text{ max}}$ in mild to severe HF classes. While the current author's calculations on data reported by Itoh et al (1989), reveal similar percentages (65-72%), with a trend towards AT occurring at *higher* percentages of $VO_{2\text{ peak}}$ with *decreasing* functional capacity. Itoh et al's data also reveals younger, healthy subjects AT occurring at slightly *lower* levels than HF patients (64-68% $VO_{2\text{ peak}}$).

There is plenty of evidence that exercise training delays the onset of blood lactate accumulation during sub-maximal exercise (Belardinelli, Georgiou, Scocco, Barstow & Purcaro, 1995; Sullivan, Higginbotham & Cobb, 1988; Sullivan & Cobb, 1990;

Hambrecht et al, 1997; Tyni-Lenné, Gordon, Jansson, Bermann & Sylven, 1997; Tyni-Lenné, Gordon, Jensen-Urstad, Dencker, Jansson & Sylven, 1999; Larsen, Aarsland, Kristiansen, Haugland & Dickstein, 2001) and it would appear that this is due to increased oxidative capacity of the skeletal muscle. Increases in size and number of mitochondria and the activity of oxidative enzymes seem to be the prime candidates for these improvements, while evidence for increased capillarisation and shifts in fibre type from glycolytic type IIb to oxidative type I is less convincing (Duscha, Schulze, Robbins and Forman, 2008).

There is conflicting evidence regarding resting lactate levels in HF patients compared to healthy individuals, with a number of studies showing no significant differences (Sullivan et al, 1989; Sullivan et al, 1991; Yamabe et al, 1994). However a number of studies report *higher* resting lactate levels in HF patients, with these high levels being noted in patients with the lowest functional capacity (Wilson et al, 1984; Schaufelberger et al, 1996; Andrews et al, 1997).

None of the studies reporting resting lactate levels following exercise training reported any significant differences between pre- and post-training levels (Sullivan et al, 1988; Sullivan and Cobb, 1990; Hambrecht et al, 1995; Belardinelli et al, 1995).

The vast majority of studies reviewed reported lactate levels in HF patients being significantly lower than healthy controls at maximal or peak exercise capacity, with the only exception being seen in exercise using a smaller muscle mass (Andrews et al, 1997). Peak lactate values were also reported to decrease with decreasing functional capacity in HF patients (Yamaba et al, 1994,; Andrews et al 1997).

Only one study (Delagardelle et al, 2002) reported increases in peak lactate values following exercise training. This result appears to be due to the different exercise mode (combined endurance/resistance) being employed in this study.

No research studies appear to have investigated blood lactate levels during cardiac rehabilitation exercise sessions, presumably due to the impracticalities of arterial and venous sampling in this setting. However, accurate and reliable lactate analysers that utilise capillary samples (Baldari, Bonavolontà, Emerenziani, Gallotta, Silva & Guidetti, 2009; Tanner, Fuller & Ross, 2010) now make this type of research feasible and ethically acceptable; the author will therefore investigate blood lactate levels of HF patients in this applied setting. More specifically, the aims of the study are:-

- 1) To investigate the acute blood lactate response of HF patients to different types of cardiac rehabilitation exercise sessions; cardiovascular and resistance.
- 2) To investigate the chronic changes in blood lactate response of HF patients following a cardiac rehabilitation exercise programme.

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Research Paper

Blood Lactate Responses of Heart Failure Patients to Cardiac Rehabilitation Exercise

Key words: cardiovascular, resistance, fingertip capillary sampling,
hand-held lactate analyser

Word count: 4360

Journal justification rationale

The journal format chosen is that of Medicine and Science in Sports and Exercise. This journal is the official journal of the American College of Sports Medicine and is multidiscipline in nature with articles enabling readers from a wide range of backgrounds to enhance their knowledge of physical activity and its role in human health and function. The articles are concise and easy to comprehend, with the use of numbered references in the text helping the flow of the article. The journal publishes papers on both heart failure and cardiac rehabilitation on a regular basis, with one of the most useful articles for this study being published in this journal.

Abstract

Purpose: The primary aim of this study was to provide cardiac rehabilitation (CR) professionals with data on acute blood lactate responses of HF patients to cardiovascular and resistance exercise during CR exercise sessions. Secondly, to quantify the chronic changes in blood lactate response to sub-maximal exercise in this patient group, as a result of a CR programme including both cardiovascular and resistance exercise. **Methods:** Nine patients with HF completed a 12 week CR exercise programme consisting of one weekly session of predominantly cardiovascular exercise (CARDIO) and one weekly session of resistance exercise (RES). Blood lactate, heart rate (HR) and ratings of perceived exertion (RPE) were determined during one session of each type. Patients completed a sub-maximal exercise test before (EXT1) and after (EXT2) the CR exercise programme, with blood lactate, HR and RPE being determined at matched workloads during each test. **Results:** Blood lactate was 20% higher in the RES session, compared to the CARDIO session, but this difference was *not* statistically significant due to the variability of response in the small patient cohort. RPE scores were not significantly different between the CARDIO and RES sessions, but HR was significantly higher ($p < 0.0001$) during the CARDIO session. Blood lactate ($p < 0.001$), HR ($p < 0.027$) and RPE ($p < 0.043$) were all significantly lower at EXT2, compared to EXT1. **Conclusion:** Blood lactate responses to CR exercise were highly variable in this patient group, but gave additional information on the exercise intensity being elicited. Blood lactate response to sub-maximal exercise at matched workloads provided an objective measure of improvements in cardiovascular fitness following a combined cardiovascular/resistance CR programme for HF patients.

Introduction

The European Society of Cardiology (McMurray et al, 2012) recommend exercise training for heart failure (HF) patients following a number of systematic reviews and meta-analyses of small-scale research studies, which have shown that training improves exercise tolerance and health-related quality of life. The large randomised controlled study HF-ACTION (O'Connor et al, 2009) also reported modest reductions in cardiac and all-cause mortality and hospitalisations.

Symptom-limited cardiopulmonary exercise testing (CPX), in order to obtain a direct measure of exercise capacity e.g. peak oxygen consumption ($\text{VO}_{2\text{peak}}$), is the gold standard method of assessing functional capacity in order to optimise the exercise prescription for individuals participating in cardiac rehabilitation (CR) exercise (Piepoli, et al, 2011). In UK CR programmes CPX is not widely used and a number of calculations are made in order to estimate the prescribed exercise intensity range using heart rate (Beale, Carter, Doust, Brickley, Silberbauer & Lloyd, 2010). The equation $220 - \text{age}$ is recommended to estimate maximum HR and a reduction of $20\text{--}30 \text{ b}\cdot\text{min}^{-1}$ is applied to account for the attenuation in HR due to the effect of beta-blockers, prior to exercise intensities being calculated as a percentage of heart rate reserve (Karvonen formula)(British Association for Cardiac Rehabilitation, 2009). However, individual differences in true maximum HR and responses to medication can lead to the recommended exercise intensity being overestimated in HF patients (Beale, Carter, Doust, Brickley, Silberbauer and Lloyd, 2010). The use of ratings of perceived exertion (RPE), alongside HR, gives additional *subjective* information on the exercise intensity, although this does require practice, particularly in patients unfamiliar with exercising

(British Association for Cardiac Rehabilitation, 2009). The measurement of blood lactate as an adjunct to HR and RPE, may give useful *objective* information on exercise intensity in this patient group.

Although numerous studies have investigated the blood lactate response of HF patients in a laboratory setting, there is currently no published research of blood lactate responses in an applied setting, i.e. during cardiac rehabilitation exercise sessions. The availability of valid and reliable portable hand-held lactate meters (Baldari, Bonavolontà, Emerenziani, Gallotta, Silva & Guidetti, 2009; Tanner, Fuller & Ross, 2010) means that this type of applied research is now feasible.

The important role that increased skeletal muscle oxidative metabolism has been seen to play in improvements in exercise capacity, coupled with the problem of muscle loss and weakness in HF, has led to increased interest in resistance exercise (Duscha, Schulze, Robbins and Forman, 2008) and resistance training is now recommended in UK CR programmes (British Association for Cardiac Rehabilitation, 2009). However, research concerning the blood lactate response to resistance exercise in HF patients is sparse.

The aims of this study were, firstly, to provide data to CR exercise professionals on acute blood lactate responses in HF patients during typical CR exercise sessions involving cardiovascular and resistance exercise. A secondary aim was to confirm and quantify the expected chronic changes in sub-maximal blood lactate levels following a CR programme for HF patients, incorporating both cardiovascular and resistance exercise training.

Methods

Patient Selection

During the study recruitment period all HF patients attending for functional exercise assessment prior to attending a Phase III cardiac rehabilitation (CR) exercise programme were invited to be part of the study. All patients were newly diagnosed with HF, or had a recent hospital admission for decompensated HF, and had left ventricular systolic dysfunction with an ejection fraction of $\leq 40\%$. All patients (n=11) were health-screened by CR programme personnel and found to be suitable to attend the Phase III CR programme for HF patients and all agreed to participate in the study. One patient subsequently failed to attend any CR exercise sessions and another discontinued attendance after two weeks, both for personal reasons. The remaining patients included in the study (n=9) were predominantly male (male = 8, female = 1), with a mean age of 66 (range 46-79) and functional classification of NYHA I (n=8) or NYHA II (n=1). All patients were treated with beta-blockers and ACE inhibitors. Beta-blocker dose changed during the study for some patients. The study protocol was approved by the NHS regional ethics committee and the research co-ordinator of the participating hospital. All patients gave their written informed consent to participate.

Exercise Testing

Patients completed a treadmill exercise test before (EXT1) and after the CR programme (EXT2). The test protocol consisted of walking at a comfortable pace, with gradient increasing at 1% each minute until a rating of perceived exertion (RPE) of 13 was reached on the RPE 6-20 scale (Borg, 1982) or the patients' heart rate (HR) reached 60% of predicted maximal heart rate reserve. Physiological measures were

taken to monitor the chronic response to the CR exercise programme. Blood lactate was determined prior to the exercise test and within one minute of the end of treadmill exercise. An additional blood lactate measurement was taken during EXT2, at a matched workload to the peak workload achieved in EXT1, to enable comparison between tests. Heart rate was assessed by telemetry (Polar F4M, Polar Electro, Oy, Finland).

Exercise Training Protocol

Patients completed a 12 week CR programme, attending two sessions per week. *Session 1 (Mondays)* consisted of resistance exercise (RES), with patients completing 2-3 sets of ~15 exercises, for 12 reps each, at a workload equivalent to 12 repetition maximum (12RM), with a rest period of 30-60 sec between sets. Exercises included upper and lower body, large and small muscle groups and included free weights (dumbbells) and resistance exercise machines. All sets of an exercise were completed before moving to the next exercise. Patients completed a 10 min warm-up and cool-down period of treadmill walking. *Session 2 (Fridays)* consisted of predominantly cardiovascular exercise (CARDIO), with patients completing 25-35 min of large muscle group endurance exercise on several ergometers (cycle, treadmill, rowing) at an individualised exercise intensity in the range 40-60% heart rate reserve (HRR) and RPE 11-13. HRR was calculated using a predicted maximum HR ($220 - \text{age}$) and subtracting $30 \text{ b} \cdot \text{min}^{-1}$ to adjust for the effects of beta-blocking medication. The endurance exercise was followed by a short resistance exercise programme consisting of 10-12 exercises for 1 set of 12 repetitions (reps) at 12RM. All patients completed a 10 min warm-up and cool-down period of treadmill walking.

Comparison of Exercise Training Sessions

Acute physiological responses to the exercise were monitored during one CARDIO and one RES exercise session. Monitoring occurred at week 3, 4 or 5 of the programme to ensure patient familiarisation with performing the exercises correctly and at the appropriate individualised target levels. *Blood lactate* was determined prior to the exercise and within one minute of the end of the main section of exercise, prior to cool-down, using capillary blood sampling as previously described. *Heart rate* was assessed by telemetry using a recordable monitor (Polar S810i, Polar Electro, Oy Finland), from the start of the warm-up to the end of the main section of exercise, prior to cool-down. Mean HR was calculated using the related software (Polar Precision Performance v4.01.029). *RPE* was assessed throughout the main section of exercise; at the end of each bout of aerobic exercise on different ergometers during the CARDIO session and at the end of the last set of each resistance exercise during the RES session.

Data Analysis

Data was analysed using SPSS software (v19.0), with statistical significance set at $p < 0.05$. Data are presented as mean \pm standard deviation (SD). Data was assessed for normal distribution using the Shapiro-Wilk statistic. Paired sample t-tests were conducted to test for differences between variables measured during EXT1 and EXT2 and during CARDIO and RES exercise sessions. Pearson's correlations were conducted to test for relationships between exercise blood lactate and appropriate variables.

Results

Acute responses to cardiovascular and resistance exercise

A summary of the parameters measured during CARDIO and RES sessions is presented in Table 1. Blood lactate was significantly higher than resting levels at the end of the CARDIO ($p<0.02$) and RES ($p<0.04$) exercise sessions. However, there was no significant difference between blood lactate levels at the end of the main section of exercise in the two types of exercise session. As resting blood lactate levels were significantly higher ($p<0.018$) prior to the CARDIO session compared to the RES session, the rise in blood lactate during exercise sessions was also compared, but was also found to be non-significant (CARDIO: $2.06 \pm 1.31 \text{ mmol}\cdot\text{l}^{-1}$; RES: $3.08 \pm 2.32 \text{ mmol}\cdot\text{l}^{-1}$).

Table 1. Acute physiological responses and workload during CR exercise sessions

Parameter	CARDIO		RES	
	Rest	Exercise	Rest	Exercise
Blood lactate ($\text{mmol}\cdot\text{l}^{-1}$)	1.77 ± 0.61	3.82 ± 1.50 §	1.49 ± 0.48 #	4.57 ± 2.08 ¥
Heart rate ($\text{b}\cdot\text{min}^{-1}$)	58 ± 5	84 ± 5	57 ± 3	76 ± 5 †
RPE		12.5 ± 0.5		12.9 ± 0.5
Workload		4.83 ± 0.94 METS		342 ± 60 reps

Data are mean \pm SD. $n=9$, except exercise HR ($n=8$) due to atrial fibrillation in one patient

METS metabolic equivalents during treadmill exercise

reps total repetitions completed

§ difference in resting and exercise blood lactate in CARDIO session ($p<0.02$)

¥ difference in resting and exercise blood lactate in RES session ($p<0.04$)

difference in resting blood lactate between CARDIO and RES sessions ($p<0.018$)

† difference in exercise HR between CARDIO and RES session ($p<0.0001$)

There was considerable variability in blood lactate at the end of both the CARDIO and RES exercise (Figure 1), therefore possible relationships between other relevant variables were investigated. No significant correlations were found *between* exercise blood lactate levels during the CARDIO and RES sessions ($r = -0.037$, $p = 0.924$)

or between resting and exercise blood lactate levels *within* each type of exercise session (CARDIO: $r = 0.495$, $p = 0.175$; RES: $r = -0.405$, $p = 0.280$). Further analysis also revealed no significant correlations between exercise blood lactate and exercise HR, RPE, workload, body mass, resting HR or age within each type of exercise session (see Table 2). It was not possible to analyse the data for correlations between exercise blood lactate levels and NYHA class due to the NYHA data not being normally distributed.

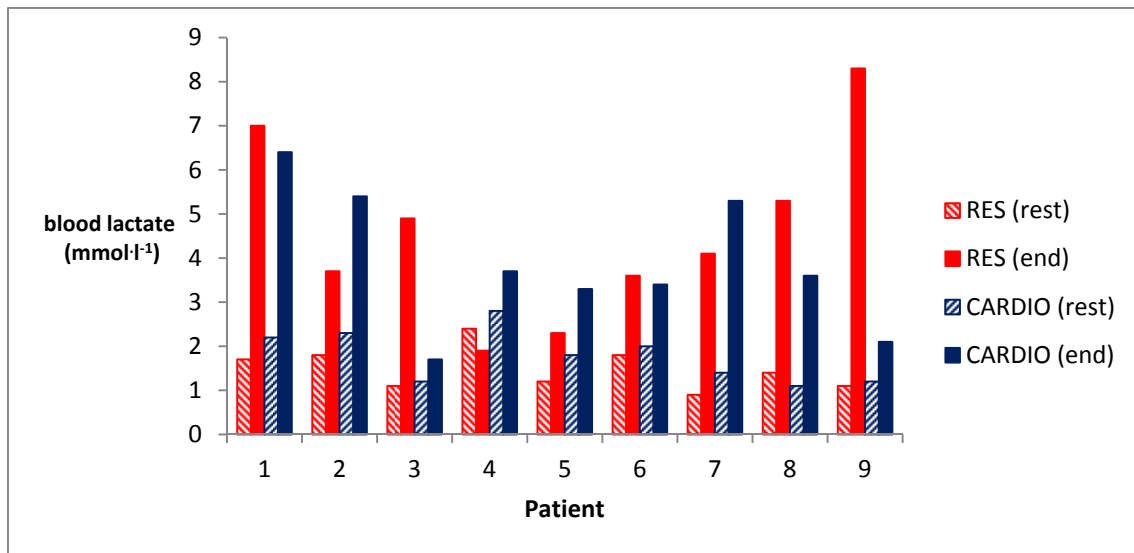


Figure 1. Individual variability in blood lactate responses during CR exercise sessions

Table 2. Pearson correlations of possible relationships between exercise blood lactate values and other relevant variables.

	Exercise HR	RPE	Workload	Body mass	Resting HR	Age
Exercise lactate CARDIO	$r = -0.044$ $p = 0.918$	$r = -0.057$ $p = 0.884$	$r = -0.464$ $p = 0.208$	$r = 0.436$ $p = 0.240$	$r = 0.125$ $p = 0.748$	$r = -0.535$ $p = 0.138$
Exercise lactate RES	$r = 0.506$ $p = 0.201$	$r = 0.595$ $p = 0.091$	$r = 0.495$ $p = 0.175$	$r = 0.636$ $p = 0.065$	$r = -0.104$ $p = 0.790$	$r = -0.405$ $p = 0.280$

r = Pearson correlation coefficient. All values non-significant at $p \leq 0.05$

Whilst there was no difference in resting HR, mean heart rate was significantly higher ($p<0.0001$) during the CARDIO session than RES. There was no significant difference in mean RPE between the two types of exercise session.

Chronic changes due to combined cardiovascular and resistance exercise training.

There was no significant difference in resting blood lactate levels between EXT1 ($1.50 \pm 0.35 \text{ mmol l}^{-1}$) and EXT2 ($1.43 \pm 0.61 \text{ mmol l}^{-1}$). The remaining data is summarised in Table 3. One patient was not included in this part of the study as the patient had not completed EXT2 by the end of the study period due to having an implantable cardiac defibrillator (ICD) fitted part-way through the CR programme. Also, one patient completed EXT2 after just 10 weeks of CR.

While there was a significant difference ($p<0.01$) between blood lactate levels at rest and peak work intensity in EXT1, there was no significant difference between lactate levels at rest and the corresponding matched workload (4.6 METS) in EXT2.

There was a significant reduction in blood lactate ($p<0.001$), HR ($p<0.027$) and RPE ($p<0.043$) between EXT1 and EXT2 at matched workloads, as well as a significant increase in peak METS ($p<0.001$). No significant differences were noted in peak blood lactate and peak HR between EXT1 and EXT2, but peak RPE was significantly higher ($p<0.014$) at EXT2.

Table 3. Chronic physiological and functional capacity changes due to a CR programme of combined cardiovascular and resistance exercise training.

	EXT 1	EXT2	
Parameter	Peak	Matched workload to EXT1 peak	Peak
Blood lactate (mmol l ⁻¹)	2.34 ± 0.53	1.63 ± 0.55 §	2.81 ± 0.90
Heart rate (b·min ⁻¹)	96 ± 10	85 ± 9 ¥	102 ± 7
RPE	12.8 ± 0.87	11.5 ± 0.93 #	13.6 ± 0.58 ‡
METS	4.60 ± 1.30	4.60 ± 1.30	6.84 ± 1.20 †

Data are mean ± SD. n=9 for EXT1 (n=8 for HR*), n=8 for EXT2 (n=7 for HR*)

*due to atrial fibrillation in one patient

METS metabolic equivalents

§ difference in blood lactate between EXT1 & EXT2 at matched workload ($p<0.001$)

¥ difference in HR between EXT1 & EXT2 at matched workload ($p<0.027$)

difference in RPE between EXT1 & EXT2 at matched workload ($p<0.043$)

‡ difference in peak RPE between EXT1 & EXT2 ($p<0.014$)

† difference in peak METS between EXT1 & EXT2 ($p<0.0001$)

Discussion

Blood lactate analysis

This study used a relatively inexpensive and portable blood lactate meter (Lactate Pro) designed to analyse whole blood from capillary samples, making it is easy to use in a cardiac rehabilitation setting. Most of the studies researching blood lactate in HF patients have used plasma, arterial blood or venous blood samples to obtain lactate levels, which would be impractical in this applied setting. Blood lactate readings from different types of sample should be compared with caution as they can differ; for example whole blood values are on average 30% lower than plasma values (Goodwin, Harris, Hernández & Gladden, 2007). Different makes and models of blood lactate analyser may also give differing results (Tanner et al, 2010; Baldari et al, 2009; Medbø, Mamen, Holt Olsen & Evertsen, 2000). Despite its small size and affordability, the

Lactate Pro meter has been shown to be valid, reliable, and at least as good as more expensive laboratory-based instruments (Medbø et al, 2000, Tanner et al, 2010). The Lactate Pro also compares well with the reference method of standard enzymatic photofluorometry, with no systematic deviations from this reference method in the low to moderate blood lactate concentrations (below 6 mmol·l⁻¹) which are commonly seen in clinical testing (Medbø et al, 2000).

Acute blood lactate responses to cardiac rehabilitation exercise

Cardiovascular exercise

As this study is, to the author's knowledge, the first to investigate blood lactate levels in an applied cardiac rehabilitation setting, and also used capillary blood samples, direct comparisons with the findings of others are problematic. However, a number of studies using similar blood sampling methods can give some context to the current findings in respect to *cardiovascular* exercise. Larsen and colleagues (Larsen, Aarsland, Kristiansen, Haugland & Dickstein, 2001) reported blood lactate levels of 2.25 ± 0.59 mmol·l⁻¹ following 30 min treadmill exercise at 85% HR maximum (~70% HRR) prior to a cardiac rehabilitation exercise programme in patients with a functional classification of NYHA III. A repeated test, following the three month exercise training period, showed blood lactate concentrations reducing to 1.95 ± 0.96 mmol·l⁻¹. Beckers et al (2012) report blood lactate levels of 3.9 ± 1.9 mmol·l⁻¹ at VO₂ peak in patients in NYHA II (33%) and III (67%) classifications. This result appears to be a mean figure for 48 exercise tests conducted at baseline, during and at the end of a cardiac rehabilitation programme. Further peak blood lactate values are reported by

Delagardelle, Feiereisen, Autier, Shita, Krecke and Beissel (2002) in patients of NYHA class II-III, with a baseline mean of $4.39 \text{ mmol}\cdot\text{l}^{-1}$.

The blood lactate levels seen at the end of the CARDIO session in the current study ($3.82 \pm 1.5 \text{ mmol}\cdot\text{l}^{-1}$) appear to be relatively high in comparison with other studies, particularly given that the prescribed exercise intensity was intended to be 40-60% HRR. The higher blood lactate values may be indicative of the higher functional capacity of patients in the current study (mainly NYHA I), as peak lactate values in HF patients have been shown to decrease with decreasing functional capacity (Yamabe, Itoh, Yasaka, Takata, & Yokoyama, 1994; Andrews, Walsh, Evans, Curtis & Cowley, 1997). Furthermore, blood lactate values of $3.0 - 4.0 \text{ mmol}\cdot\text{l}^{-1}$ are indicative of 'moderate exercise', i.e. below the 2nd lactate threshold, in healthy participants (Binder et al, 2008). However, it should be noted that three patients had blood lactate levels that were well above this ($4.8, 5.4$ and $6.4 \text{ mmol}\cdot\text{l}^{-1}$), which might indicate either that they were exceeding the prescribed exercise intensity, or the prescribed exercise intensity was too high. However, mean RPE values for these patients during the cardiovascular exercise were within the target range of RPE 11-13 (11.75, 12.5, 12.9 respectively). An alternative explanation may be that blood lactate values were elevated due to the resistance exercises performed as part of the CARDIO exercise session, usually after the main cardiovascular exercise had been performed. As, although not statistically significant, blood lactate values were 20% higher following the RES session compared to the CARDIO session.

Resistance and cardiovascular exercise comparison

There appears to be no previously published data on the *acute* blood lactate responses to resistance training in HF patients, with which to compare the results from this study. In the current study, blood lactate was 20% higher at the end of the RES exercise compared to CARDIO, but this difference was not statistically significant, presumably due to the highly variable responses (see Figure 1), with blood lactate levels being higher following the RES session in only five out of nine patients. A confounding variable in this analysis is the difference in resting blood lactate levels prior to the exercise sessions, for which there appears to be no obvious explanation, apart from the sessions being held on different days of the week. It should be noted that the rise seen between resting blood lactate and exercise blood lactate was much greater in the RES session, being 50% higher than the rise in blood lactate seen in the CARDIO session, but again this difference was not statistically significant.

No relationships were found between exercise blood lactate levels and other parameters measured in this study, so the data collected does not offer any explanation for the variability in blood lactate levels between patients. It might have seemed plausible that patients with higher *resting* blood lactate levels exhibited higher *exercise* blood lactate levels, or that patients with higher blood lactate levels in the CARDIO session might exhibit higher levels in the RES session, but the data does not support these speculations. A possible explanation for the higher blood lactate levels noted in some patients following the RES exercise, is that these patients might have had a relatively greater muscle mass and/or a greater proportion of type II muscle fibres, and were therefore able to produce more lactate. Muscle atrophy is a hallmark of HF, particularly in the elderly, with a CHF-induced reduction in type I fibres adding to

the type II fibre decrease seen due to ageing (Volaklis and Tokmakidis, 2005). The higher blood lactate levels could perhaps be due to patients being less debilitated by HF, or perhaps having more muscle mass/greater proportion of type II fibres due to resistance training prior to a HF diagnosis. Additionally, the motivation of the patient and their willingness to endure the discomfort caused by higher blood lactate levels may also have had some effect. Further research, involving patients with a greater range of functional capacity (NYHA classification) and including measurement of lean body mass, is needed to investigate these theories.

Although the patients' perception of effort, as seen in the RPE scores, is similar for both the CARDIO and RES exercise, the mean HR exhibited in the RES session was 8 $\text{b}\cdot\text{min}^{-1}$ lower than the CARDIO session, suggesting less cardiovascular stress due to resistance exercise. However, the additional measurement of blood pressure in order to calculate rate-pressure product ($\text{HR} \times \text{systolic blood pressure}$) would have given a better indication of the overall haemodynamic response to these two types of exercise session (Volaklis and Tokmakidis).

Blood lactate levels and sympathetic nervous system activity

Strong positive relationships between blood lactate levels and the catecholamines epinephrine/norepinephrine have been reported during exercise (Belardinelli, Georgiou, Scocco, Barstow and Purcaro, 1995; Tyni-Lenné, Gordon, Jensen-Urstad, Dencker, Jansson, and Sylven, 1999) and epinephrine/norepinephrine concentrations are reported to rise rapidly above lactate threshold (Wasserman, 1989). Therefore, it might be prudent to conduct lactate threshold testing prior to patients' attendance at CR exercise sessions, in order to ensure the exercise intensity

prescribed is truly of 'moderate' intensity, i.e. below the 2nd lactate threshold (Binder et al), thus ensuring that sympathetic nervous system activity is not unduly elevated. This seems particularly pertinent given the issue of over-estimation of exercise intensity reported by Beale and colleagues (Beale et al, 2010).

Chronic changes due to combined cardiovascular and resistance exercise training

At rest

Resting blood lactate levels were unchanged following the CR exercise programme in this study and these findings are consistent with those previously reported (Sullivan, Higginbotham and Cobb, 1988; Sullivan and Cobb, 1990; Hambrecht et al, 1995; Belardinelli et al, 1995).

During sub-maximal exercise

Blood lactate levels at a sub-maximal workload (60% HRR at EXT1) were significantly reduced, by around 30%, following the CR exercise training programme in this study, indicating a reduced reliance on anaerobic metabolism and consequently a raised anaerobic/lactate threshold. This finding is in agreement with the numerous other studies examining the effects of exercise training on this patient group (Belardinelli et al 1995; Sullivan et al, 1988; Sullivan & Cobb, 1990; Hambrecht et al, 1997; Tyni-Lenné, Gordon, Jansson, Bermann & Sylven, 1997; Tyni-Lenné et al, 1999; Larsen et al, 2001). The majority of the studies cited have used aerobic endurance (cardiovascular) training programmes. Belardinelli et al reported a 20% increase in lactate threshold following a low intensity (40% VO₂max) exercise programme and Larsen et al noted a 19.5% decrease in blood lactate, utilising an endurance exercise

test protocol, following a higher intensity (80% HR max) programme. Although it is difficult to make direct comparisons due to the many differences in training programmes (duration, frequency and intensity) and functional classification of patients, the results of the current study certainly seem to provide support for the efficacy of a combined endurance/resistance training programme for this patient group in respect of improvements in anaerobic threshold. Previous studies looking at chronic changes to sub-maximal blood lactate response due to *resistance training* or *combined endurance/resistance training* in HF patients are sparse. Tyni-Lenné et al (1997) reported a 17% reduction in blood lactate levels during sub-maximal exercise following a programme of knee extensor training, while the study by Delagardelle et al, which compared a combined endurance/resistance training programme with endurance training alone, reported only peak lactate values. However, increases in anaerobic threshold due to combined endurance/resistance training have previously been noted in patients with coronary artery disease (Hansen, Dendale, Berger & Meeusen, 2005).

Heart rate was reduced at the matched sub-maximal workload following the CR exercise training programme, indicating improved cardiac performance, which has been extensively reported previously (Piepoli, 2013). However, it should be noted that changes in beta-blocker dosage made during the study may have had some effect on the reported heart rates. The lowered blood lactate and HR were reflected by the reduced effort perceived by the patients, as measured by RPE ratings.

At peak workload

It should be noted that peak parameters reported in this study were *sub-maximal* (60% HRR) 'end of test' values and so cannot be compared with previous research in which investigators have reported peak values that were symptom-limited *maximal* values.

Peak RPE was significantly higher during the post-programme exercise test (EXT2), suggesting that patients felt they were working significantly harder than at the pre-programme test (EXT1), even though the exercise intensity end-point was theoretically the same. There was also a trend towards higher peak HR and peak RPE values at EXT2, although these were not statistically significant. These findings may be due to the increased confidence of CR staff when exercising patients following the CR programme, allowing patients to work slightly harder than prior to the CR programme, when patients are newly referred. This tester bias may lead to a slight over-estimation of the increases in functional capacity (peak METS) reported. The measurement of blood lactate at fixed sub-maximal workloads may therefore provide an additional objective measure of the efficacy of CR exercise training, which is unaffected by changes in medication, or tester bias.

Study limitations

This study looked at blood lactate responses in a relatively small group of HF patients, consisting predominantly of men with a relatively high level of functional capacity (NYHA I). Further, larger studies including more women and a greater range of functional capacity (NYHA II-III) are needed to investigate whether these findings can

be applied to other groups of HF patients. Future studies might include monitoring of blood pressure and lean body mass, as mentioned previously.

A number of methodological decisions were made in order to minimise the disruption to the patients during the CR programme. Firstly, during the CARDIO session, a number of resistance exercises were included as this was part of the normal CR programme. It may have been advisable to test the blood lactate prior to performing the resistance exercises to exclude any effect from these and ensure the blood lactate response reflected only the cardiovascular exercise. However, patients would often perform the resistance exercises interspersed throughout the session, so this was not possible. A second limitation is the slight difference in the timing of the blood lactate sampling at matched workloads during EXT1 and EXT2, as patients were at rest following the exercise test during the sampling procedure for EXT1, but were still exercising at the matched workload during the sampling procedure for EXT2. This may have led to minor differences in blood lactate readings.

Conclusion

This small study provides some initial findings for CR professionals on the acute blood lactate responses elicited in HF patients during cardiovascular and resistance exercise training sessions, which seem to be quite variable between patients. Furthermore, it demonstrates that blood lactate sampling is practical within the applied setting of CR exercise sessions and may identify patients that are exercising at an intensity that is above the prescribed level. In addition, the study provides support for the monitoring of chronic changes in blood lactate levels during sub-maximal exercise testing as an additional objective measure to quantify the efficacy of a CR

exercise programme in terms of the reduced reliance on anaerobic metabolism due to increases in cardiovascular fitness.

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